extracellular surface of the cell or partially embedded in the cell membrane. One of skill in the art would also understand that the term "membrane-associated" would include those antigens within the cell membrane or on the intracellular surface of the cell membrane. Such association would be understood to include association with the cell membrane and associated cytoskeletal elements. Again, the term "membrane-associated" is well used and well know in the art. As such, the term is definite. Accordingly, withdrawal of the rejection is respectfully requested.

Rejection under 35 USC 103

Claims 1-4, 6-11, and 13-17 have been rejected under 35 USC 103 as allegedly being obvious over Hajek et al. in view of Fodstad et al. and O'Briant et al. Applicants respectfully traverse the rejection.

The Examiner stated that according to Hajek, it seems that cell clumping only occurs at high concentration of cells. Thus according to the Examiner, one of skill in the art would have been motivated to use cell suspension in the method of Hajek, taught by Fodstad and Hajek with an expectation of success, because using cell suspension or smearing for cell visualization under microscope are methods that are interchangeable, give the same results, and are well known in the art.

However, the Examiner appears to be impermissibly using hindsight in stating that one would have used the teachings of Hajek et al. to arrive at the present invention. Hajek teaches away from visualization in suspension, suggesting it is inferior to visualizing cells smeared on a slide (see, *e.g.*, column 3, lines 61-64 of Hajek et al.). Further, Hajek et al. teach that clumping can occur in suspension, which is incompatible with the presently claimed method (it is incompatible because of the steric hindrance and quenching problems created by clumping). Nothing in Hajek et al. would suggest one of skill in the art to visualize cells in suspension, and Hajek et al. in fact teach away from the presently claimed invention.

Further, the Examiner is incorrect in stating that using cell suspension or smearing for cell visualization under microscope are methods that are interchangeable. First, Hajek et al., as stated above teach away from the use of visualization in cell suspension because one cannot obtain the same type of morphological characterization as with cells smeared on a slide. Thus, the Hajek et al. patent itself teaches that these methods are not interchangeable. Further, the presently claimed method would not be effective if cells were visualized as a smear on a slide.

This is because producing a smear will destroy the binding and also produce loss of target cells, as the cells will not adhere properly to the glass since they are surrounded by beads. Lack of adhesion would be detrimental to the presently claimed invention as relatively few cells with a population are being detected. A loss of cells could mean that no cells would be detected, giving a false negative. Clearly, using cell suspension or smearing for cell visualization under microscope are not interchangeable methods.

Further, the Examiner stated that Hajek et al. teaches that clumping occurs at only high concentrations. However, the Examiner is discounting the fact that as the number of different particles with different associated antigens increase, the amount of clumping would be expected to increase. Surprisingly, the inventors found that their claimed method could be performed without clumping. In fact, the inventors have shown that they can achieve a lack of clumping when using four different particles with different associated antibodies. Such a result is clearly unexpected in light of Hajek et al.

The Fodstad patent does not overcome the deficiencies of the Hajek patent. The Fodstad patent teaches the appropriate conditions for detecting specific target cells when using a single paramagnetic particle associated with a single antibody species. However, as stated above, as the number of particles with different associated antibodies is increased, one would expect clumping of cells in suspension, and clumping is not compatible with the claimed method. Fodstad does not teach that clumping can be avoided when using multiple particles as required by the present claims. In light of Hajek, which does teach that clumping can occur, one would not use the teachings of the Fodstad patent in combination with the teachings of the Hajek patent to arrive at the presently claimed invention.

O'Briant et al. does not cure the deficiencies of the Hajek and Fodstad patents. The Examiner appears to cite O'Briant et al. for the proposition that breast cancer cells, and apparently other cancer cells, can express multiple antigens and that the use of multiple antibodies may be preferred over the use of a single antibody. However, O'Briant et al. do not teach how one would avoid the clumping problem that the inventors surprisingly cured with the presently claimed method.

Hajek et al. teach away from the presently claimed invention by indicating that visualization in suspension is inferior to visualization on a slide after smearing. Further, Hajek et

al. do not teach or suggest how to solve the clumping problem, the likelihood of which increases as additional different particles with different associated antibodies are used. In addition, the combination of the Fodstad patent and O'Briant et al. does not cure the deficiencies of Hajek et al. As such, the presently claimed invention is not obvious over the combined teachings of Hajek et al., Fodstad, and O'Briant et al. Withdrawal of the rejection is respectfully requested.

Conclusion

With the above amendments and remarks, Applicants believe that the claims now pending in this patent application are in a condition for allowance. Favorable consideration is respectfully requested. If any further questions arise, the Examiner is invited to contact Applicants' representative at the number listed below.

Respectfully submitted,

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